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The immunological synapse: required for T cell receptor signalling or directing T cell effector function?

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The discovery of the immunological synapse is one of the more striking developments in T cell biology in recent years. The immunological synapse forms at the interface between T cells and antigen-presenting cells (APCs) or target cells. It is characterised by the large-scale segregation of cell surface molecules into concentric zones, forming a bull's eye pattern several microns in diameter (reviewed in [1]). In their excellent review of recent work on the immunological synapse, published in *Current Biology* [2], Delon and Germain correctly stress, as we have [1], that synapse formation follows, and is dependent on, T cell antigen receptor (TCR) signalling. Although this indicates that synapse formation is not required for TCR signalling, they nevertheless conclude, as have others [3], that a principal function of the synapse is to "stabilise signal transduction by the TCR for the prolonged periods of time required for gene activation" [2]. As we discuss below, recent work suggests that the dynamics of TCR signalling are likely to be profoundly altered by synapse formation. Rather than being important for TCR signalling, we argue that immunological synapse formation is linked instead to the delivery of secondary T cell signalling and effector functions, such as directed secretion. The protein kinase p56lck,

which phosphorylates the TCR upon antigen engagement, and the phosphatase, CD45, which maintains p56lck in a primed or activatable state, are both required for TCR signalling [1]. Kinetic models [4–6] predict that signalling will be highly sensitive to the distances over which such molecules have to diffuse to reach their substrates. According to recent studies [7,8], there is no visible segregation of the TCR from CD45 at the time when TCR signalling peaks, shortly after antigen encounter. This situation changes dramatically upon synapse formation, however, whereupon CD45 is excluded from the 0.5–1 μM central region within which the TCR and p56lck are sequestered. It is highly unlikely that the enzymology of TCR triggering accommodates two kinetically distinct signalling mechanisms, or one mechanism that is dependent on CD45 and another that is not. Rather than sustaining signalling, therefore, the observed reorganisation seems to us more likely to be detrimental to TCR signalling. It is a formal possibility that the dramatic images of the synapse exaggerate the degree of molecular segregation and that TCR signalling continues unabated after synapse formation. However, this would still imply that the gross structural features of the synapse have little to do with TCR signalling.

What then might the purpose of the immunological synapse be? A key role for this structure emphasised in earlier studies is directed secretion, which focuses effector functions, such as cytokine secretion and cell killing, on the antigen-presenting or target cell, reducing bystander effects [9,10]. We propose that directed secretion is linked to large-scale molecular segregation at the synapse for two reasons. First, in order for the effects of directed secretion to be restricted to the presenting or target cell it is important that the granule contents of the T cell be retained at the interface. The narrow interface and adhesion ring around the central portion of the synapse may serve this purpose and explains why cytokine receptors are relatively small. Second, it seems likely that remodelling of the cytoskeleton accompanies, and is required for, directed secretion, and that associated cell-surface molecules become segregated as a consequence of these processes. Support for a link between synapse formation and directed secretion is provided by the recent demonstration that, at the interface between cytotoxic T cells and their targets cells, secretory granules congregate next to, and release their contents into, the central portion of the synapse [11].

Although synapse formation may favour processes other than TCR signalling, this does not rule out a critical role for the synapse in signalling, particularly via receptors other than the TCR. Significantly, the expression of cytokine receptors or the involvement of co-stimulatory molecules appear to be better correlates of the rate of T cell commitment by naïve and effector cells, than levels of TCR triggering *per se*, as measured by TCR internalisation [12]. A clear temporal and functional correlation exists between T cell–APC conjugation, synapse formation and T cell activation which is readily explained by secondary signalling processes involving, for example, cytokine–cytokine receptor and co-stimulatory receptor–ligand interactions. These processes will be enhanced by extended cell–cell contact and are likely to depend on the cytoskeletal rearrangements and directed secretion that are the hallmark of synapse formation [1].

TCR signalling is perhaps best viewed as the first in a series of obligatory checkpoints leading to full T cell activation and commitment. Rather than being the site of prolonged TCR signalling, the synapse seems to us more likely to mediate both the secondary signalling events leading to full T cell activation and the delivery of T cell effector functions.

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